C. Remarks

The claims are 24-38, with claim 24 being the sole independent claim. Claim 24 has been amended to address a minor informality. Applicants submit that no new matter has been added. Reconsideration of the present claims is respectfully requested.

Claims 24-38 stand rejected for obviousness-type double patenting in view of claims 1, 2 and 4-16 of U.S. Patent No. 6,726,928. As noted in the previous response, Applicants respectfully traverse this rejection, but in an effort to expedite prosecution of this case, it is Applicants' present intention to file a terminal disclaimer to overcome this rejection when all the other issues have been resolved.

Claims 24, 26-30, 32-34 and 36 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over *Gregory* (U.S. Patent No. 4,305,502) in view of *Ince* (U.S. Patent No. 4,657,929). Claims 24-34 and 37 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Gregory* in view of *Mughal* (U.S. Patent No. 4,465,838). Claims 35 and 38 stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Gregory* in view of *Kurazumi* (U.S. Patent No. 5,182,112). Applicants respectfully traverse these rejections.

At the outset, Applicants would like to incorporate by reference herein the entirety of the previously set forth arguments regarding the deficiencies of *Gregory* as a primary reference. Those arguments make the point that there is simply no teaching in *Gregory* concerning a positive step of rendering an active substance less soluble. As such a step is explicitly required in the presently amended claims, it is respectfully submitted that claim 24 and its dependent claims are clearly distinguishable over *Gregory* whether viewed alone or in any combination with *Ince, Mughal* or *Kurazumi*.

Applicants believe that the Examiner may be under a misconception about the present invention. More particularly, the Examiner has taken the position that "[t]he

method of formulation of a pharmaceutically active agent into a readily dissolving, orally administered tablet taught by Gregory et al. has the inherent property of rendering the active substance less soluble and more palatable." The presently claimed process of preparation does not itself render a pharmaceutically active agent less soluble. Instead the preparation process of the present invention utilizes a pharmaceutically active agent which has been rendered less soluble. In other words, none of presently claimed steps (b) through (d) are responsible for the pharmaceutically active agent's being less soluble; instead the pharmaceutically active agent is rendered less soluble by some definitive action on the formulator's part and then utilized for the presently claimed process in step (a). In this way, it can be seen that the basic formulation process of *Gregory* could not inherently render an active substance less soluble.

Beyond this, Applicants respectfully submit that the Examiner's present position is not scientifically sound. Solubility of a solid substance refers to the concentration of the substance in a liquid that has reached equilibrium with the substance in the solid phase (i.e., adding more solid to the mixture will no longer increase the concentration of the liquid phase). Solubility is a characteristic of a substance. The manufacturing process taught by *Gregory* removes the solvent from a liquid mixture, thereby producing a solid dosage form. This process itself does not alter the solubility of the substance, which is an inherent property of the substance, but merely produces a change in form. For example, sugar in hot water dissolves to form a liquid sugar solution, but the solubility of sugar does not change.

The present invention discloses a process whereby the unacceptable taste may be rendered less soluble by conversion of a salt to a free acid. An active ingredient is selected that is inherently less soluble, i.e, a free base form as opposed to an alkaline salt form, but that has the same pharmacological effect. Because the present claims are method

claims, the art must teach or disclose the steps of the presently claimed method. *Gregory* is completely deficient in this regard. And, in fact, its stated preference for highly soluble pharmaceuticals teaches away from such a method step ("it is desirable that when the chemical is added to the aqueous medium the chemical should dissolve rapidly" at column 1). Applicants submit that it is not obvious to those ordinarily skilled in the art to achieve the taste masking process of the present invention by using a step of rendering a pharmaceutically active substance less soluble based on *Gregory* and any of the secondarily cited references. Indeed, none of the secondary references *Ince, Mughal* and *Kurazumi* remedy the basic deficiency of *Gregory*.

Ince is cited by the Examiner for its disclosure related to domperidone; the Examiner alleges that *Ince* utilizes domperidone free base, but Applicants find no such disclosure therein. Regardless, *Ince*'s use of domperidone does not remedy *Gregory*'s deficiency because, again, there is no teaching of a positive step of purposefully using/choosing to use a pharmaceutically active agent which has been rendered less soluble. Since the present claims are method claims, this point is not insignificant. While domperidone can be used in a "less soluble" form, i.e., as the free base, there is no acknowledgment of that in *Ince*, no preference to use such a less soluble form in *Ince*, and no indication that such a less soluble form would be suitable for use in a rapidly disintegrating dosage form such as disclosed by *Gregory*.

Mughal teaches the formation of a more palatable form of oxaprozin by selection of a less soluble salt. However, it, too, fails to remedy the deficiencies of *Gregory* since it would be counterintuitive for one of ordinary skill in the art to combine the teachings of *Gregory* and *Mughal*. More particularly, given *Gregory*'s logical preference for readily soluble active ingredients in the formation of rapidly disintegrating dosage forms, one of ordinary skill in the art would not look to decrease the solubility of

the intended active as such a step would seem to be opposed to the desired end point. *Gregory*'s disclosure of the use lorazepam does not teach otherwise. There is simply no disclosure of selecting lorazepam in a form based on its solubility. Unlike these references, the present invention specifically selects a less soluble form of a substance that has exactly the same pharmacological effect and uses that less soluble form to make a rapidly disintegrating dosage form.

Kurazumi teaches a method of enhancing the anti-diarrheal efficacy of loperamide by adding a saccharide in an amount 3,000 to 20,000 times the weight of loperamide. According to the FDA Orange Book, the only strength of loperamide listed is 2 mg. Therefore, a minimum of 6,000 mg of saccharide must be included in any formulation. A skilled formulator would not attempt to formulate this into the dosage form of *Gregory*. For example, in Example 1 of the specification of the subject invention, 1.759 g of mannitol is used to formulate loperamide, equivalent to 2.93 % w/w mannitol. To accommodate 6,000 mg mannitol in the final formulation, each tablet before drying would weigh 204,778 mg, and the size of the finished tablet would be approximately 200 ml. Such a tablet is not practical to manufacture and certainly is not attractive to consumers.

Further, the Examiner alleges that sodium bicarbonate is disclosed in the formulation of *Kurazumi*, and, for this reason, it is implicit that this component was used to render the drug less soluble. However, as discussed above, a skilled pharmaceutical formulator would not contemplate combining the teachings of *Kurazumi* with *Gregory*. Furthermore, *Kurazumi* also teaches the use of citric acid in Examples 1, 2, 3 and 4. The addition of citric acid enhances the solubility of loperamide rather than reducing it. Therefore, looking at *Kurazumi* with *Gregory* in their entirety, a skilled practitioner would not arrive at the subject invention, i.e., a process for the preparation of a solid, oral, rapidly

disintegrating dosage form of a pharmaceutically active ingredient with an unacceptable taste by rendering the active substance less soluble.

In sum, no combination of *Gregory, Ince, Mughal* and *Kurazumi* renders the present invention obvious. Simply put, the cited prior art fails to disclose or suggest certain key features of the present invention, namely positive steps of rendering an active substance with an unacceptable taste less soluble and formulating that less soluble active substance in a fast dissolving dosage form. For at least these reasons, Applicants submit that no combination of *Gregory, Ince, Mughal* and *Kurazumi* renders the present claimed invention obvious and respectfully request withdrawal of the §103 rejection.

In view of the foregoing amendments and remarks, Applicants respectfully request favorable reconsideration and allowance of the claims in the present application.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our below listed address.

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